Bye, bye, bile: how altered bile acid composition changes small intestinal lipid sensing

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The gastrointestinal (GI) tract is increasingly recognised as a major contributor to energy homoeostasis that impact obesity progression. The gut represents the first site of interaction between incoming nutrients and the host, generating crucial negative feedback signalling to regulate food intake possibly by altering GI function like gastric emptying. In the case of proximal intestinal lipid sensing, several mechanisms have been identified to drive both satiety and satiation. For example, dietary fat is hydrolysed and absorbed into enterocytes. In the upper GI, this stimulates the synthesis of oleoylethanolamide (OEA), which can then act as a signalling molecule to induce satiety via activation of peroxisome proliferator-activated receptor-α and a gut-brain axis.[1] Alternatively, activation of enteroendocrine cells (EECs) by free fatty acids binding to G protein-coupled receptor-40 leads to secretion of gut peptides, like cholecystokinin and glucagon-like peptide-1 (GLP-1), which slow gastric emptying and reduce food intake. Interestingly, activation of EECs via free fatty acids is hypothesised to occur on the basolateral side, requiring chylomicron formation, and thus dietary fat hydrolysis, similar to OEA production.[2] Given that bile acids, especially cholic acid in mice, emulsify dietary lipids and thus promote efficient hydrolysis and absorption of lipids in the small intestine, their function would implicate a necessity in activating the aforementioned pathways to lower food intake.

In *GUT*, Higuchi *et al* observed that Cyp8b1$^{-/-}$ mice exhibited reduced body weight and adiposity due to an inhibition of food intake. As expected, lowering cholic acid and other 12α-hydroxylated bile acids via 12α-hydroxylase Cyp8b1 knockout impairs dietary fat absorption. However, they elegantly deciphered the mechanism explaining the unexpectedly decreased body weight and reduced food intake by identifying that the gastric emptying incurred by a lower intestinal lipid-gut peptide signalling axis.[3] Cyp8b1$^{-/-}$ mice exhibited reduced body weight and adiposity due to an inhibition of food intake. Mechanistically, Cyp8b1$^{-/-}$ mice actually had decreased refed jejunal OEA levels, therefore increased intestinal OEA signalling leading to increased satiety is not the driving mechanism for reduced food intake. This is in line with the fact that Cyp8b1$^{-/-}$ mice exhibited reductions in meal size, and not inter-meal interval, suggesting the decrease in food intake is via increased satiation and not satiety. Instead, the authors attributed the reduction in meal size to slowed gastric emptying. First, the authors established this reduction in gastric emptying was lipid-dependent, as feeding of a fat-free diet abolished the reduced food intake and gastric emptying in Cyp8b1$^{-/-}$ mice. Second, the authors established slowed gastric emptying was mediated via GPR119 signalling, as both acute pharmacological inhibition of GPR119 in Cyp8b1$^{-/-}$ mice and genetic knockout of GPR119 (via double knockout) normalised the gastric emptying defect, while double knockout mice exhibited no difference in body weight, adiposity or food intake. Third, reduced gastric emptying was dependent on a combination of peptide YY (PYY) and GLP-1 signalling, and importantly, the authors demonstrated that this was likely downstream of GPR119 activation, as double knockout mice (GPR119 and Cyp8b1) abolished the increase in ileal PYY and GLP-1 levels observed in Cyp8b1$^{-/-}$ mice following a fasting-refeeding study. Thus, the study concluded that reduced adiposity in Cyp8b1$^{-/-}$ mice is due to increased presence of distal small intestinal lipids, potentially activating an ileal GPR119-GLP-1 and –PYY axis that slows gastric emptying to reduce food intake.[3]

One major question left unanswered is what promotes the activation of GPR119 in distal intestine in the current study. Given that several pharmacological GPR119 agonists are being tested for treatment of metabolic disease, a better understanding of how altering bile acid composition can lead to increased GPR119 signalling is of therapeutic relevance. Indeed, while OEA can activate GPR119, it was unlikely the case as jejunal OEA levels were decreased in Cyp8b1$^{-/-}$ mice.[3] Given that Cyp8b1$^{-/-}$ deficiency causes impaired hydrolysis of ingested triglycerides, there is an increased amount of lipids reaching the distal intestine.[4] Therefore, it is possible that the enhanced influx of 2-monoacylglycerol to the ileum could activate EECs as 2-monoacylglycerols are a ligand for GPR119,[2] although this was not directly tested via direct intraileal infusion at levels observed in Cyp8b1$^{-/-}$ mice. However, GPR40, which binds free fatty acids, is also present on EECs and contributes to gut peptide secretion, and at least one study demonstrates a synergistic effect of GPR119 and GPR40 signalling in GLP-1 secretion.[5] Thus, it would be interesting to determine if GPR40 also plays a role in the aforementioned pathway regulating gastric emptying. Furthermore, it has been recently hypothesised that GPR40 activation leading to gut peptide release takes place on the basolateral side of the EECs, requiring chylomicron formation in nearby enterocytes;[2] it remains unknown if this effect on ileal GPR119 is via direct luminal action on the apical side or whether it also requires chylomicron formation and subsequent activation on the basolateral side.

In the current paper, the authors did not determine if Cyp8b1$^{-/-}$ mice in all the experimental conditions have changes in glucose homoeostasis in addition to alterations in adiposity, as Cyp8b1$^{-/-}$ mice has been documented to exhibit improved glucose homoeostasis.[4] It would be an interesting area to expand on as small intestinal lipid sensing increases intravenous glucose tolerance and lowers hepatic glucose production in rats and mice independent of changes in food intake,[6 7] which raises the possibility that enhanced ileal lipid sensing and subsequent increased GPR119-GLP-1 signalling axis in Cyp8b1$^{-/-}$ mice may lead to improved glucose homoeostasis. The relative contribution of intestinal bile acid receptor farnesoid x receptor (FXR) signalling is another component that could be explored in the current experimental context, as inhibition of intestinal FXR increases GLP-1 secretion, and Cyp8b1$^{-/-}$ mice have reduced FXR activation due to a shift in bile acid composition favouring

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non-efficacious versus efficacious ligands of FXR.[8] However, how inhibition of FXR in Cyp8b1$^{-/-}$ mice contributes to GLP-1 release in the ileum remains to be assessed. Furthermore, this underscores a critical component of the overall GI landscape that warrants further investigation: the gut microbiota. There exists an intrinsic relationship between the gut microbiota and bile acids, and Cyp8b1$^{-/-}$ mice do have an altered gut microbiota composition.[9] Thus, it would be interesting to determine what role Cyp8b1$^{-/-}$ mice gut microbiota has in the overall effect on gastric emptying, given that the gut microbiota has previously been linked to gut motility and transit.[10]

Overall, Higuchi *et al*[3] identify the intestinal mechanism regulating reduced food intake in Cyp8b1$^{-/-}$ mice via slowed gastric emptying. Interestingly, treatment of wild type mice with non-12-hydroxylated bile acids, which are high in Cyp8b1$^{-/-}$ mice, resulted in decreased fat absorption and lowered gastric emptying compared with treatment with cholic acid, which is absent in Cyp8b1$^{-/-}$ mice. This highlights the therapeutic potential of altering the composition of bile acid pools in metabolic diseases via activation of ileal lipid sensing mechanisms.

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